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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/464,902	12/16/1999	WILLIAM C. OLSON	57906-AJPW/S	8227

7590 01/13/2005

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/464,902	OLSON ET AL.	
	Examin r	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/12/04*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *87,88,91-95,98-100 and 102-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *87-88, 91-95, 98-100 and 102-109* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Claims 102-109 are added. Claims 87-88, 91-95, 98-100 and 102-109 are pending and under examination.

Allowable Subject Matter

2. Claims 91-92, 98, 102, 105-106 and 108 contain allowable subject matter, nucleic acids that encode a polypeptide that corresponds to at least six CDR regions of an antibody or a polypeptide that binds to an epitope of CCR5, wherein the epitope comprises amino acid residues in (1) an N-terminus of CCR5, (2) one of the three extracellular loop region of CCR5, or (3) a combination thereof.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 87-88, 93-95, 99-100, 103-104 and 107-108 are rejected under 35 U.S.C. 112, first paragraph for being enabling for isolated nucleic acid molecule t that encodes a minimum of 6 CDR regions of the deposited antibodies. Additionally, claims 87-88, 93-95, 99-100, 103-104 and 107-108 would be deemed allowable if Applicant amends the claims to recite a specific binding activity, such as incorporating the limitations recited in claim 91 into the rejected claims.

Applicant maintains that the claimed invention is fully enabled by the specification as filed. Applicant submits that not all six CDRs bind to the target antigen, while pointing to Desmyter et al. and Davies et al. for support. Desmyter et al. teaches that only the

CDR3 region of a single domain anti-carbonic anhydrase antibody interacts directly with the antigen. Davies et al. teaches that in the interaction between influenza virus neuraminidase and the NC10 antibody, only four of the CDRs in the NC10 contact the antigen.

Applicant also submit that it has long been established that a peptide sequence as short as a single CDR can bind immunospecifically to an epitope and exhibit functional activity characteristic of the intact antibody, while directing the Examiner's attention to the teaching of Williams et al. (1989), Taub et al., Williams et al. (1991), and Bourgeois et al. for support. Applicant further emphasize that not only can single CDR sequences bind to a target epitope but they can also exhibit the biological activity of the intact antibody, directing at Bourgeois et al. for support. Bourgeois et al. teaches that a peptide sequence corresponding to a singe CDR of a neutralizing antibody against respiratory synctial virus (RSV) inhibits RSV infectivity both in vitro and in vivo with the same subgroup neutralizing specificity as the antibody.

Additionally, Applicant contends that the fact a particular mutation in a CDR causes a significant effect on antigen binding in no way implies that any change in amino acid sequence of the CDR would result in the detriment of antibody binding. Several studies have indicated that many changes in the amino acid sequence within a CDR have little effect on the antigen-binding function of a CDR, while pointing to Parhami-Seren et al. for support. Parhami-Seren et al. teaches that whereas two particular mutations in HCDR2 of an antibody, 36-71, resulted in significant loss of binding, all other mutations in HCDR2 had minimal effect on antibody affinity.

Applicant's submission has been considered, however, it is not found persuasive. The issue at hand is that the skilled artisan in the art would not be able use the full scope of the claimed invention without and undue burden of experimentation. Applicant has not taught the skilled artisan how to use polypeptides that corresponds to one CDR region or portions thereof of an antibody. The skilled artisan would not be able to use the full scope of the claimed invention without an undue burden of experimentation, as demonstrated by Williams et al. (1989 and 1991). Williams et al. encompasses two references that Applicant has cited to demonstrate that the claimed invention is enabling for the nucleic acid molecules that encode peptides that correspond to a minimum of one CDR region of an antibody. While Applicant is correct to note that Williams teaches of peptides that corresponds to a CDR region of an antibody, however, Applicant has neglected to note that Williams et al. teaches that a peptide that is directed to a CDR region of a light chain does not exhibit the same activity as that of its corresponding full antibody. The peptide does not inhibit DNA replication, whereas its corresponding full antibody inhibits DNA replication. It is only after modification is made to the peptide sequence that Williams et al. was able to demonstrate that the peptide exhibit biological activity. Williams et al. also notes, in other studies, a peptide that corresponds to the heavy chain variable regions fail to exhibit biological activity similar to that of its corresponding antibody. William et al. does not teach the skilled artisan how to use peptides based on antibody CDR region structures. Williams et al. only teaches how to make these peptides, wherein only modified versions of these peptides exhibit similar biological activity as that of its corresponding antibody. Williams et al. does not demonstrate that the peptides, modified or non-modified, have the same biological activity as its corresponding antibody would

command. Like Williams et al., Bourgeois et al. notes the same. Bourgeois et al. is a reference that is cited by Applicant to demonstrate the peptides to a CDR region can bind to a target antigen and exhibit biological activity of the intact antibody. In the instant, Bourgeois et al. teaches that of the six CDRs, only one CDR have neutralizing activity that is similar to that of its corresponding antibody.

Applicant is correct to note that in some species, functional single-domain antibodies naturally lack light chains and contain only three CDR loops contributed by the heavy chain; however, the stated presentation is not applicable and relevant for the claimed invention. The polypeptides of antibodies to which the claimed nucleic acid molecules encode are directed at conventional antibody molecules, specifically murine antibodies, not camelid antibodies. Murine antibodies differ from camelid antibodies structurally. Murine antibodies naturally consist of two light chains and two heavy chains, and consists of three CDRs for each chain; whereas camelid antibodies is a functional single-domain antibodies that naturally lack light chains and contain only three CDR loops.

In the instant, contrary to the teaching of Taub et al. and Bourgeois et al., Applicant has failed to teach the skilled artisan in the art how to use the full scope o the claimed invention without an undue burden of experimentation. The difference between the instantly claimed invention and the polypeptides to antibodies that it encode is that Taub et al. and Bourgeois et al. teach the skilled artisan how to use their specific peptides without an undue burden of experimentation. In both instances, Taub et al. and Bourgeois et al. are specific to a particular CDR region that each recognizes as important to the biological activity that they chose to observe. In the instant, Applicant provides no such correlative analysis. If anything, the teaching of Taub et al. and Bourgeois et al. only further

exemplify the amount of experimentation that the skilled artisan must conduct to practice the full scope of the claimed invention.

The Examiner agrees with Applicant that even in an antibody consisting of heavy and light chains and comprises six CDRs, not all these CDRs necessarily bind to the target antigen, however, all six CDRs must be present to maintain the antigen binding specificity and affinity. In the instant, Davies et al., a reference cited by Applicant to demonstrate that not all six CDRs necessarily bind to the target antigen, recognize the importance of all six CDRs. Davies et al. experimented with the Fab portion of an antibody, which comprises a light chain and heavy chain—each of which contains three CDRs, thus, totaling six CDRs.

Lastly, it appears that Applicant has taken the teaching of Rudikoff et al. and the Examiner's summation of the teaching of Rudikoff et al. out of its intended context. In the instant, the Examiner relies on the teaching of Rudikoff et al. to demonstrate the level of unpredictability in the antibody art is extremely high, while pointing to Rudikoff et al. for support. Rudikoff et al. teaches that even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function. Applicant further affirms this level of unpredictability with presentation of teachings by Parham-Seren et al. Parhami-Seren et al. teaches that two mutations in a CDR region of an antibody resulted in significant loss of binding.

In the instant, Applicant has not taught the skilled artisan how to use polypeptides that are encoded by the claimed nucleic acid molecules that corresponds to less than six CDR regions of an antibody. Currently, the listed claims are directed to a multitude of polypeptides that the skilled artisan would not know how to use without an undue burden of experimentation. In conclusion, Applicant is reminded that the above lack of

enablement analysis is based on the culmination of the factors set forth in the previous office action, Wands factors, in view of the discussion above and the level of unpredictability that is associated with the instant antibody art, the claimed invention remains rejected for not being enabling for its full scope.

Conclusion

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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